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Respiratory muscle unloading during auto-adaptive non-invasive ventilation☆

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Summary
Rationale: Non-invasive ventilation (NIV) has been shown to improve clinical outcomes in acute and chronic hypercapnic respiratory failure. A new timed, automated, auto-adaptive non-invasive ventilatory mode (TA-mode) has been recently introduced.
Objective: To investigate the degree of respiratory muscle unloading with this new mode in comparison to assisted (S-mode) NIV in healthy individuals.
Methods: Work of breathing, pressure time product and transdiaphragmatic pressure time product were measured during unassisted breathing, assisted and TA-mode-NIV in eight healthy, awake volunteers at inspiratory pressures of 20 and expiratory pressures of 4 hPa.
Results: Assisted and TA-mode-NIV reduced the work of breathing by 50 and 89.1%, pressure time product by 61.5 and 72.6% and transdiaphragmatic pressure time product by 77 and 88.7%, respectively when compared to unassisted breathing. The degree of respiratory muscle unloading was higher during TA-mode-NIV when compared to assisted non-invasive ventilation (work of breathing $p < 0.001$, pressure time product $p = 0.04$ and transdiaphragmatic pressure time product $p = 0{,}01$).
Conclusion: TA-mode-NIV achieved significant higher levels of respiratory muscle unloading in healthy individuals when compared to assisted non-invasive ventilation.
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Introduction

There is robust evidence that non-invasive ventilation (NIV) decreases work of breathing, improves gas exchange and relieves dyspnea in acute and chronic respiratory failure.[1–4] NIV unloads the respiratory muscles and thereby increases patient mobility[5] and endurance.[6] The degree of respiratory muscle unloading depends on the ventilatory mode as well as on the level of ventilatory support.[7–9]

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Trigger sensitivity determines the energy that has to be spent before the ventilator will support the breathing cycle.[10,11] Work to trigger the ventilator can be substantial and is reported to be as high as 65% of the work of passive inflation during invasive ventilation[12–14] and up to 39% during NIV.[15] During assisted mode ventilation patient effort does not abruptly cease with the onset of gas delivery by the ventilator and muscle effort is still present after the ventilator has started to support the breath.[13] Reduction of the breath initiating effort is likely to increase the degree of respiratory muscle unloading. This could be achieved by application of controlled ventilator modes during NIV. Controlled NIV is feasible[16] but carries the risk of patient–ventilator asynchrony with increased workload during inspiration and expiration.[17,18] A new ventilator mode (TA = timed automated adaptive mode, Weinmann, Hamburg, Germany) has been introduced into the market.[19] This mode is programmed to analyse and closely follow the patients' own respiratory pattern in a controlled fashion.

The present study compares the TA mode to the commonly used assisted mode during NIV by measuring the degree of inspiratory muscular unloading in healthy and awake individuals to confirm or refute the presence of more effective respiratory muscle unloading.

Method

The institutional review board (Medical Association, Wilhelms University Muenster, Germany, application No. 2006-532-f-S) approved the protocol. From previous unpublished data we estimated Cohen's d to be 3.14 and the effect size to be 0.84.

Power analysis (Gpower 3.0.10) determined the number of required measurements to be $n = 7$. We recruited eight healthy volunteers (one female) and obtained informed consent. Lung function tests were performed using a body plethysmograph (Masterlab, Jaeger, Wuerzburg, Germany). Subject characteristics are shown in Table 1.

For each individual a suitable face mask was selected and adjusted to achieve optimal air tightness and comfort. Preferably, nose-masks were selected, however a full face mask was necessary in one individual to accomplish optimal fit. Volunteers were positioned in a 45 degree upright position using a recliner chair. Two balloon catheters (47-8605, Ackrad Laboratories, Cranford, NJ, USA) were introduced through the nostrils and advanced with aid of active swallowing into the stomach. Catheters were passed through the mask by means of two small bore holes which then were sealed with plastinate to achieve air tightness (Fig. 1). We connected catheters to capacitative pressure transducers (DP 15-36,Validyne, Northridge, CA, USA) connected to an amplifier (CD223, Validyne, Northridge, CA, USA). A flow sensor (4700 Series, 0-160 LPM, Hans Rudolph Inc., Kansas City, MO, USA) was attached between mask and whisper valve and connected to a pneumotach amplifier (1110, Hans Rudolph Inc, Kansas City, MO, USA). We captured data on a personal laptop computer using a customized Lab View Program (Version 6, National Instruments, Austin, TX, USA) after A/D conversion (PMD-1208LS converter, Meilhaus Electronics, Puchheim, Germany) at a sampling rate of 100 Hz.

Table 1 Demographic and lung function data, forced expiratory volume in one second (FEV_1), vital capacity (VC).

	Mean	±SD
Age (years)	38	9
BMI	22.6	2.6
FEV_1 (l)	4.8	0.5
FEV_1% predicted	112.4	11.4
VC (l)	5.6	0.6
VC % predicted	104.1	11.7

We calibrated the catheters after inflation with 2.5 cc of air and retracted one catheter until we obtained opposing pressure signals and confirmed position with the occlusion method.[20]

Ventilator equipment, pressures and modes

We used a Ventilogic non-invasive ventilator (Weinmann, Hamburg, Germany).

We selected an inspiratory pressure (P_I) of 20 hPa for the following reasons: (1) NIV in chronic hypercapnic patients has been shown to be effective above a threshold of 18 hPa.[21] (2) Selecting pressures higher than 20 hPa have resulted in marked hyperventilation of the healthy volunteers.[22] We selected the lowest possible expiratory pressure (P_E, 4 hPa) in the absence of airway collapse.

These settings resulted in an effective driving pressure of 16 hPa, a number shown to be effective in hypercapnic patients.[21]

Modes

We applied NIV using assisted (S = Spontaneous) as well as TA mode ventilation.

During assisted ventilation inspiratory and expiratory trigger sensitivity was set to 5 (possible range 1–6, 6 being most sensitive), P_I was set to 20 hPa and P_E to 4 hPa.

We measured the effort during unassisted breathing with the subjects breathing spontaneously through the flow sensor attached through the mask while the NIV-tubing system was disconnected.

Description of TA mode

To set up the TA mode one has to select P_I, P_E, a target respiratory rate and a range of allowance as well as the type of expected underlying disease (R = Restrictive, O = Obstructive, N = Normal). The TA mode begins with an analysis phase. During this phase, a continuous pressure of 4 hPa is maintained to guarantee effective carbon dioxide washout through the whisper valve. During this phase, the ventilator analyzes the patients own flow profile by integration of flow and time (Fig. 2). Once the ventilator senses a stable profile (time and flow measurements within a predefined range of allowance), the ventilator will increase P_I over five consecutive breaths in steps of 60–70–80–90–100% of preset P_I (Fig. 2). During the inspiratory phase, P_I will be adjusted over

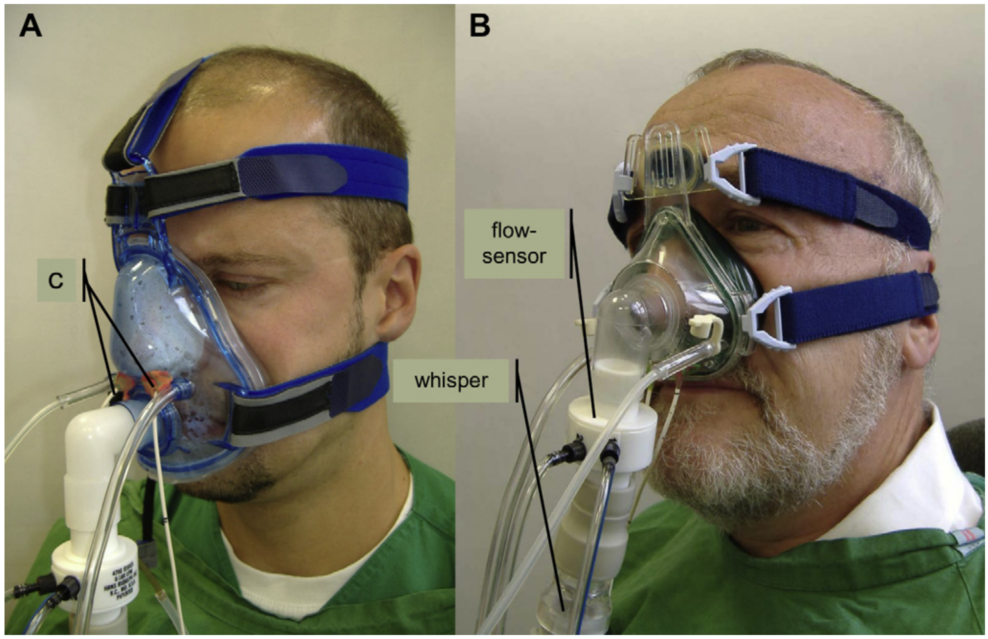

Figure 1 Experimental setup with full face mask (A) and nose mask (B). Esophageal and gastric catheters (C) are passed through small bore holes, sealed with plastinate. A flow-sensor is attached distal to the whisper valve.

inspiratory time in order to obtain a flow profile matching the patients' own pattern.

The inspiratory pressure curve is being calculated according to the following motion equation (equation (1)):

$$P(t) = R \times \text{flow} + 1/C \times \text{volume} \quad (1)$$

$P(t)$ represents the pressure integral, flow and volume arise from averaged flow pattern data from the analysis phase. The selection R = Restrictive, O = Obstructive and N = Normal allocates distinct constant numbers for resistance (R given in hPa/(l/s)) and compliance (C given in ml/hPa) into the equation (Table 2). The system software calculates $P(t)$ according to the individual pre-selected maximal inspiratory pressures.

Inspiratory time refers to the average inspiratory time recorded during the analysis phase. We selected a broad range of the respiratory rate to allow each individual to achieve his or her natural respiratory rate. The target rate—range selection can be used to prevent an inept and non-physiological breathing pattern.

Inspiratory to expiratory time ratio (I:E ratio) is determined by the subjects' I:E ratio measured during the

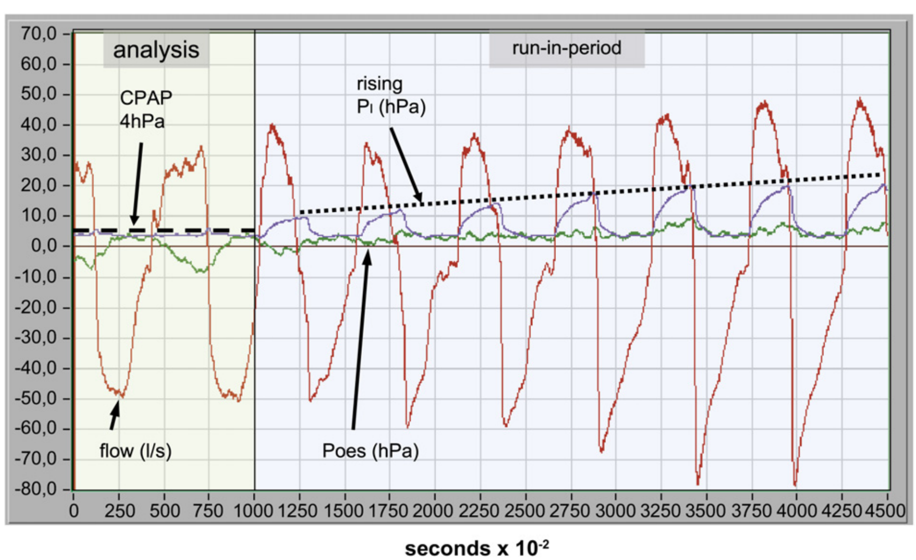

Figure 2 Pressure and flow tracings during the analysis phase and run in period of auto-adaptive controlled ventilation (TA-mode). According to the measured flow profile of spontaneous breathing, the ventilator slowly increases inspiratory pressure (P_I) during the run in period, resulting in increased inspiratory flow (flow) and raised esophageal pressure (Poes), a marker of respiratory muscle unloading.

Table 2 Selection of the type of underlying disease changes the values for resistance and compliance in the motion equation [$P(t) = R \times \text{flow} + 1/C \times \text{volume}$].

	Resistance hPa/(l/s)	Compliance ml/hPa
$R_{estrictive}$	2	40
$O_{bstructive}$	8	70
N_{ormal}	4	70

analysis phase. TA mode does not allow for additional triggered breaths, however if the ventilator senses subject—ventilator asynchrony, it will reanalyze the patients flow pattern. Asynchrony is defined by inspiratory and/or expiratory fighting in four consecutive breaths. Inspiratory fighting is defined by a flow reduction of at least 20 l/min below the mean inspiratory flow inside the middle 60% of the inspiratory time (between T_I20 and T_I80). Expiratory fighting is defined by the presence of flow rise of 10 l/min above leak-compensation inside the middle 40% of the expiratory time (between T_E30 and T_E 70).

Measurements, data analysis and assessment of respiratory effort

We recorded all data during a 5-min period following a 5 min interval of stabilization (respiratory rate and minute-ventilation ±5%). Our software compiled one data set for each 30 sec interval including esophageal and gastric pressure, flow as well as time.

We performed offline analysis of data sets using a customized software module based on the lab-view software version 6.0 (National Instruments, Austin, TX, USA).

Chest wall compliance (Ccw) was estimated to be 4% of vital capacity per hPa.[23] To exclude leak flow during the experiment inspiratory and expiratory volume for each breath, we had to match with an allowance of less than ±3% per breath.

The module was programmed to calculate the following parameters:

1. Total inspiratory work of breathing (WOB) was calculated from the area between the inspiratory pressure volume curve and the line of chest wall compliance using esophageal pressure tracings. The interception of the Ccw line with the X-axis was set to the point of inspiratory flow onset for lower bound calculation and to the point of expiratory flow cessation for upper bound calculation. We calculated WOB in joule per litre of ventilation.
2. Total inspiratory pressure time product (PTP) was measured as the time integral of the difference between the esophageal pressure tracing and the recoil pressure of the chest wall. The latter was calculated by multiplying the estimated Ccw and measured inspiratory volume. PTP is expressed in hPa*s/l.
3. Inspiratory transdiaphragmatic pressure time product (PTPdi) was calculated by subtraction of gastric from esophageal pressure. PTPdi is defined as the total area of the resulting curve below baseline. PTPdi is expressed in hPa*s/l.
4. Parameters that define respiratory pattern such as tidal volume (VT in litres), respiratory rate (f_R in breath per minute), minute ventilation ($\dot{V}$ in l/min) and inspiratory time (T_I in %)

We calculated PTP and PTPdi according to upper and lower bound criteria. For upper bound the marker was set to the beginning of rapid decrease of the pressure curves whereas lower bound marker was set to onset of inspiratory flow.[24] As expected, in the absence of airway disease upper and lower bound measurements did not differ and we limited data presentation to lower bound measurements.

We randomized the order of the three different runs (unassisted breathing, assisted-mode and TA-mode).

Statistics

Differences for the three different runs were evaluated by means of one-way ANOVA (Scheffé procedure for post hoc analysis).

Results

PTP, PTPdi and WOB for unassisted breathing, assisted-mode and TA-mode supported breathing are shown in Figs. 3—5. Compared to unassisted breathing, assisted as well as TA-mode ventilation achieved significant reductions in all three measured parameters ($p < 0.001$). The level of remaining respiratory muscle work during TA-mode ventilation was lower compared to assisted-mode ventilation ($p < 0.05$ or less, see figures for details).

Table 3 shows to what extent PTP, PTPdi and WOB have been reduced during assisted and TA-mode ventilation. As

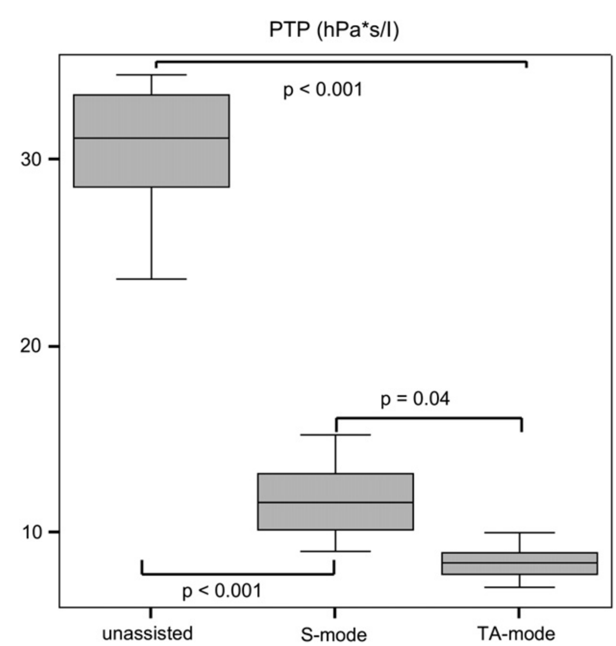

Figure 3 Pressure time product (PTP) during unassisted breathing, S-mode and TA-mode non-invasive ventilation.

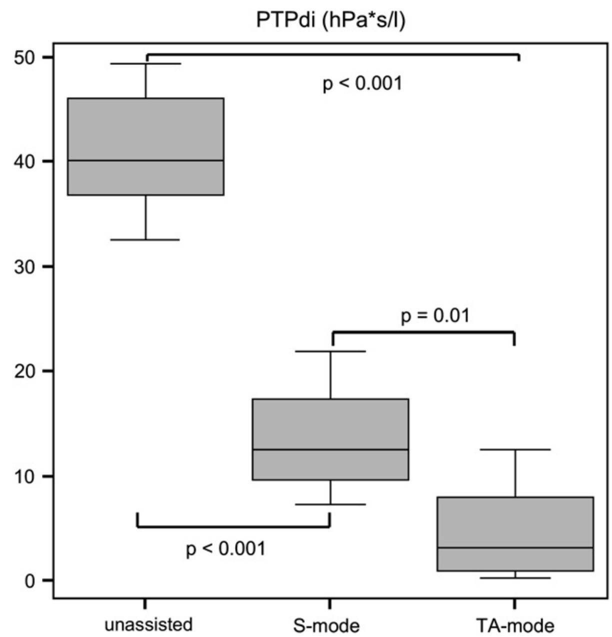

Figure 4 Pressure time product of transdiaphragmatic pressures (PTPdi) during unassisted breathing, S-mode and TA-mode non-invasive ventilation.

expected in healthy individuals, the addition of NIV increased V_T and $\dot{V}$ (Table 4). We also observed an increase in fB. During the period of data collection, we found no ineffective triggering or subject ventilator asynchrony by manual analysis of the pressure and flow curves.

Discussion

TA-mode NIV significantly decreases respiratory muscle load when compared to assisted-mode NIV in healthy awake individuals. The reduction of the respiratory workload is considerable and reaches almost up to 90% when compared to spontaneous breathing and up to 39% in comparison to assisted ventilation depending on the examined variable. Our variables (WOB, PTP and PTPdi) measure muscular effort throughout the inspiratory portion of the breathing cycle. Previous studies in patients with COPD have shown, that the respiratory muscle effort, necessary to activate the inspiratory trigger is already estimated to be somewhere between 26 and 39%.[15] Total inspiratory muscular unloading of ventilator modes avoiding trigger effort could therefore exceed this number in the presence of obstructive airway disease.

With the results displayed in table four it becomes evident, that inspiratory time during TA mode ventilation correlates quite well to the inspiratory time during unassisted breathing. This was not unexpected, since one major objective of TA mode ventilation was to deliver a flow-pattern, that matches the patients or subjects own flow pattern at a slightly higher respiratory rate. To achieve this goal the software algorithm will adjust the inspiratory pressure during each breath in order to match the previously measured target flow profile. This implies that the programmed inspiratory pressure during TA mode ventilation will only be reached at peak inspiratory flow, whereas inspiratory pressure during assisted ventilation will be held throughout the whole inspiratory time. The latter mechanism and the higher subject effort during assisted ventilation resulted in more pronounced hyperventilation in our healthy subjects (Table 4).

We did not observe subject-ventilator asynchrony during our measurements. Previous studies have shown that inappropriate termination of the mechanical inflation can increase the workload of the succeeding breath and might cause ineffective triggering and asynchrony in the presence of increased expiratory resistance.[18,25] There is an absolute

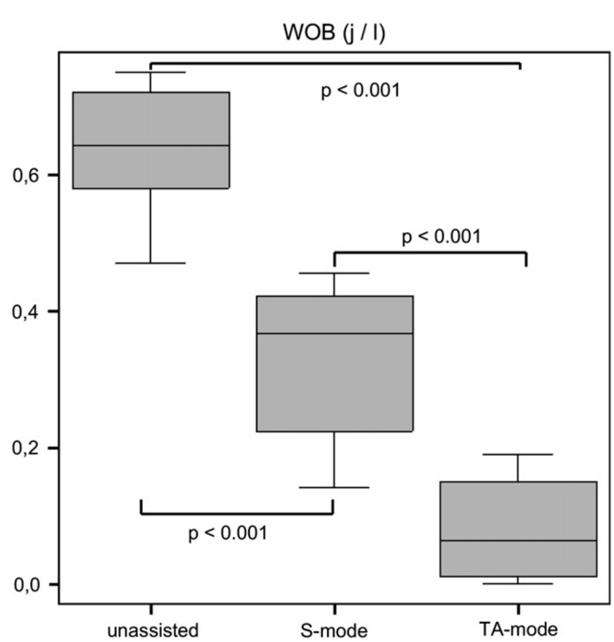

Figure 5 Work of breathing (WOB) during unassisted breathing, S-mode and TA-mode non-invasive ventilation.

Table 3 Pressure time product (PTP, hPa*s/l), pressure time product of transdiaphragmatic pressures (PTPdi, hPa*s/l) and work of breathing (WOB, j/l) have been reduced by the different forms of NIV to the percentage given in this table.

	PTP	PTPdi	WOB
Unassisted	100%	100%	100%
S-mode NIV	38.5%	33%	50%
TA-mode NIV	27.4%	11.3%	10.9%

Table 4 Tidal volume (V_T), respiratory frequency (f_R), minute ventilation ($\dot{V}$) and inspiratory fraction (T_I) during unassisted breathing as well as assisted (S-mode) NIV and auto-adaptive (TA-mode) NIV. Inspiratory pressure 20 and expiratory pressure 4 hPa.

	V_T (l)	f_R (min^{-1})	$\dot{V}$ (l/min)	T_I (%)
Unassisted	0.7 ± 0.15	11.7 ± 2	7.9 ± 1.1	45.9 ± 2.4
S-mode NIV	1.4 ± 0.38	13.2 ± 2.7	17.5 ± 3.6	40.6 ± 5.6
TA-mode NIV	1.0 ± 0.3	14.8 ± 2.3	14.7 ± 3.7	45.3 ± 2.4

need to evaluate, if such mechanisms are present in TA-mode ventilated patients. Invasive measurements in chronic respiratory failure (CRF) patients during different sleep stages as well as clinical data are necessary before recommendations for the use of TA-mode ventilation can be given.

NIV improves respiratory muscle performance by supporting and resting respiratory muscles during periods of ventilation.[1,26–28] The level of pressure support is probably the most important variable determining respiratory muscle unloading. This might be the reason why some investigators failed to find positive effects of NIV in CRF [3,29,30] using lower pressures while others found improvements using higher inspiratory pressures.[3,16,31]

The total extent of muscular unloading during NIV is being defined by the degree of muscular unloading during, and the time of NIV application.

No study so far has investigated the optimal composition of these two parameters and it is likely that optimal composition is dependant on disease type and severity.

Complete respiratory muscle unloading however has been associated with development of diaphragmatic dysfunction (VIDD).[32]

In our experiments, we were not able to completely suppress respiratory muscle activity with either mode of ventilation. This may be different, when ventilatory response decreases during sleep,[33] especially in patients with respiratory failure.[34] The role of NIV induced VIDD has still to be defined and should be viewed in regard of degree and time of muscular unloading during NIV in future studies.

Conclusion

Auto-adaptive controlled NIV increases the degree of respiratory muscle unloading when compared to assisted NIV in our experiments in awake and healthy individuals. Invasive measurements in patients with respiratory failure and clinical data are necessary to define the future role of TA-mode ventilation.

Conflict of interest statement

D. Dellweg has received fees (500 €) and T. Barchfeld has received fees (750 €) from Weinmann for lectures on the matter of subject.

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